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Unusual metastasis of gastrointestinal stromal tumor misdiagnosed as anaplastic thyroid carcinoma

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Introduction

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumors of the digestive tract. Almost all GISTs express the KIT protein (CD 117), the product of the c-KIT protoncogene that is a transmembrane receptor for the stem cell factor (SCF or KIT ligand) with a tyrosine kinase domain. The tumorigenesis of GISTs involves mutations in the c-KIT protoncogene, resulting in ligand-independent constitutive activation, i.e. activation in the absence of SCF of the tyrosine kinase receptor KIT. About 70–80% of the GISTs are also positive for CD34 and approximately 30% are positive for Smooth Muscle Actin (SMA), whereas a large majority of tumors is negative for S-100 protein and desmin.[1] Metastatic spread of GISTs is usually to the liver, omentum and/or peritoneum as emphasized by Barnes et al.[2] in their interesting review.

Case report

A 69-year-old man was referred to the Medical Department of ''La Sapienza University'' for

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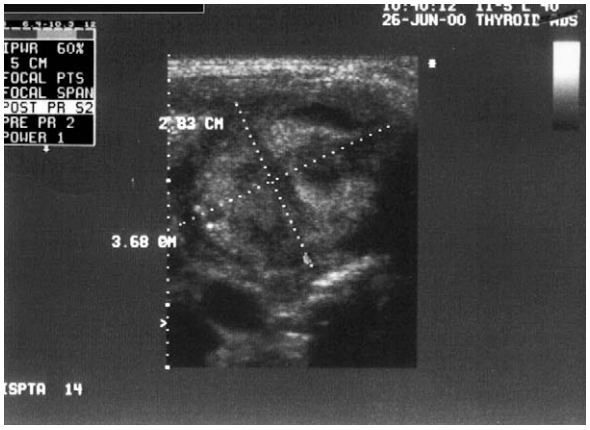

Figure 1 Ultrasonographic image of the right thyroid lobe mass.

evaluation of weight loss, asthenia, and fits of dry cough and dyspnea. Physical examination and several imaging procedures, including chest and thoracic inlet X-ray, cervical ultrasonography, cervical and thoracic CT scan, revealed a multinodular plunging goiter with left tracheal dislocation because of a prevalent nodule of the right thyroid lobe (Fig. 1). An iron deficiency anemia (Hb: 10.5 g/dl) was revealed by routine blood tests. Normal values of the serum level of FT3, FT4, TG, TSH, calcitonin and antithyroid peroxidase antibodies were present; the values of blood gas and the ventilatory function tests resulted in the normal range. The patient did not consent to esophagogastroduodenoscopy (EGDS). No masses were demonstrated by colonoscopy, abdominopelvic ultrasonography, and abdominopelvic CT. In August 2000 a total thyroidectomy was performed at the Department of Surgical Sciences of ''La Sapienza University''. Definitive histology revealed a colloid cyst and an hyperplastic benign nodule in the left thyroid lobe and a largely necrotic anaplastic carcinoma (Fig. 2a) 5 cm in maximum size confirmed by immunohistochemical negativity for calcitonin (CT), carcinoembryonic antigen (CEA), neuron-specific enolase (NSE), chromogranin A (CgA), thyroglobulin (TG), and cytokeratin (CK). In the postoperative course, because of increasing inappetence and onset of dyspepsia, the patient consented to EGDS: endoscopic biopsies of an ulcerated polypoid mass that was revealed at the lower third of the stomach were suggestive of a poorly differentiated carcinoma. Twenty days after thyroidectomy, a subtotal gastrectomy and a jejunal resection were performed because the surgical exploration revealed a little jejunal mass that at frozen section examination showed a stromal tumor. Pathological examination showed a necrotic polypoid brown-dark ulcerated mass, 5.5 cm $\times$ 3 cm $\times$ 2 cm in size,

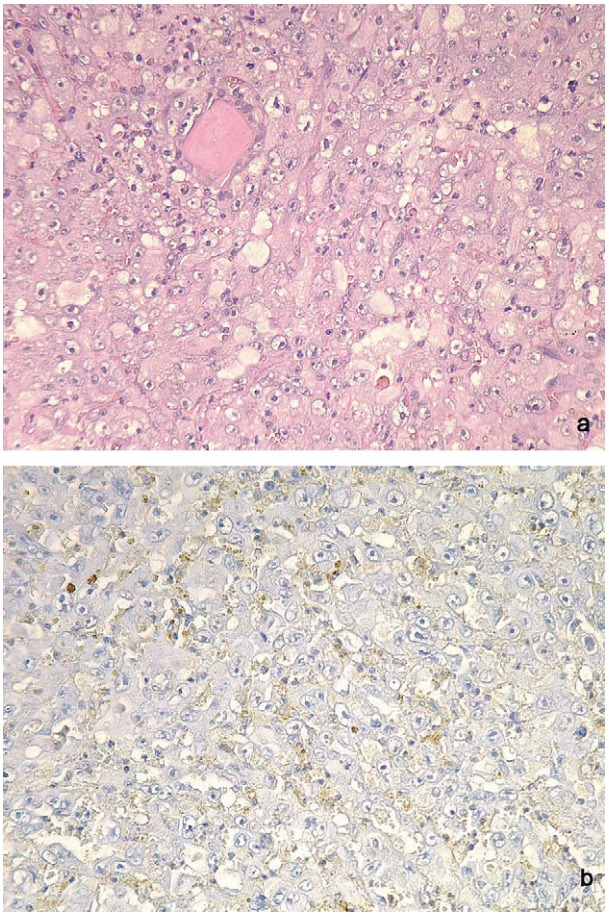

Figure 2 (a) Hematoxylin—eosin stain. Right thyroid lobe mass diagnosed as anaplastic carcinoma; (b) immunohistochemistry. Right thyroid lobe mass: focal positivity for c-KIT suggestive for GISTs.

infiltrating full-thickness the lower gastric wall and a protruding ulcerated mass, 1.2 cm in greatest diameter penetrated full-thickness the jejunal wall. Histological examination of the formalin-fixed specimen indicated that gastric and jejunal masses were stromal cell neoplasms with high mitotic rate ($>5 \times 50$ high power fields) showing lymphatic and venous invasion and immunohistochemical focal positivity for VIM, CD34, c-KIT, S-100 and SMA and immunonegativity for CK and LCA. Definitive diagnosis of gastric and jejunal high-grade GISTs was made and the morphological and immunophenotypical features of the diagnosed anaplastic thyroid carcinoma were reconsidered. Based on the microscopic features of the revised histological sections and on the additional immunohistochemistry showing diffuse positivity for VIM, focal positivity for c-KIT (Fig. 2b), CD34, S-100 and SMA and negativity for LCA, the thyroid tumor was reinterpreted as a synchronous thyroid metastasis from high-grade GISTs. The patient died nine months later because of neoplastic spread.

Discussion

Recent progresses in medical treatment of GISTs indicate that STI571 (Imatinib mesylate) therapy is effective in metastatic and recurrent GISTs: the tyrosine kinase inhibitor, STI571, selectively suppresses the activity of ABL, PDGFR and KIT tyrosine kinases. Heinrich et al.[3] suggested that GISTs express KIT or PDGFRA oncoproteins and also that KIT and PDGFRA mutations are mutually exclusive oncogenic events in GISTs and have similar biological consequences; thus GISTs also showing low or undetectable KIT expression but strongly PDGFRA expression could be sensitive to Imatinib. Nunobe et al.[4] showed that in metastatic GISTs, surgical treatment seems to be difficult due to the high frequency of repeated metastasis to various sites, therefore, they pointed out that adjuvant therapy must be required in the treatment of metastatic GISTs. In the study by Bauer et al.[5] viable tumor cells were found in all but one resected specimen of patients with metastatic GIST treated by preoperative Imatinib therapy suggesting that despite favorable radiological or clinical responses, Imatinib is unlikely to induce pathological complete response. However, an early aggressive surgery is indicated for patients with metastatic GISTs until definitive results from prospective trials investigating a combined surgical and pre- or postoperative Imatinib treatment are available.[2,5] The importance of a multidisciplinary approach using both surgery and Imatinib therapy is also emphasized in the study by Heinrich and Corless.[6] Pathological complete response after Imatinib treatment was reported in a metastatic gastrointestinal stromal tumor.[7] Barnes et al.[2] pointed out that Imatinib therapy can inhibit neoplastic proliferation and induce shrinkage of metastatic GIST enabling resection and that surgery remains an important treatment in metastatic GIST providing the best palliation and eliminating the resistant neoplastic clones. Irving et al.[8] reported five cases of ovarian metastasis of GISTs: most of these were initially misdiagnosed as tumors of other types with significant therapeutic and prognostic implications because of medical treatment now available for GISTs.

To our knowledge, this is the first report of thyroid metastasis spreading from gastrointestinal stromal tumors. Unfortunately, when our patient was treated, the benefits of the Imatinib therapy for metastatic GISTs were not yet known.

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